# Head-to-head comparison of $^{18}$F-FDG versus $^{18}$F-FAPI-74 PET in radioactive-iodine refractory differentiated thyroid cancer patients

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## Abstract

**Objective:** Fibroblast activation protein inhibitor (FAPI) positron emission tomography/computed tomography (PET/CT) was reported to outperform fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT in thyroid cancer in heterogenous patient collectives. This interim analysis of a prospective study aims to determine whether $^{18}$F-FAPI-74 is superior to $^{18}$F-FDG PET/CT in the distinct subgroup of radioactive-iodine (RAI)-refractory differentiated thyroid cancer (DTC). **Subjects and Methods:** Ten patients with recurrent DTC, detected by elevated thyroglobulin, negative RAI-scan after thyroidectomy and RAI-therapy were prospectively included. All patients underwent $^{18}$F-FAPI-74 and $^{18}$F-FDG PET/CT. The diagnostic performances were compared on a per-patient and per-lesion basis. **Results:** Fluorine-18-FAPI-74 PET/CT missed tumour recurrence in one patient. Fluorine-18-FDG PET/CT revealed more metastases in three patients. No management change following $^{18}$F-FAPI-74 PET/CT was documented. On a per-lesion analysis, the quantitative uptake values were significantly higher for $^{18}$F-FDG than $^{18}$F-FAPI-74 in all metastases ($^{18}$F-FDG: median tumor to background ratio-TBRmax: 3.05 (1.02-9.55), $^{18}$F-FAPI-74: median TBRmax: 1.09 (0.38–5.09); P<0.001) ($^{18}$F-FDG: median TBRmean: 1.71 (0.65-11.53), $^{18}$F-FAPI-74: median TBRmean: 0.64 (0.24-3.20). The detection rate was significantly higher for $^{18}$F-FDG (29/71) compared to $^{18}$F-FAPI-74 PET/CT (13/71, P<0.001). **Conclusion:** Fluorine-18-FDG-PET/CT outperforms $^{18}$F-FAPI-74 PET/CT in RAI-refractory DTC in this prospective analysis.

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## Introduction

Poorly or de-differentiated thyroid cancer is associated with poorer survival rates as compared to differentiated thyroid cancer (DTC). Fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) serves as the gold standard imaging method in radioactive iodine (RAI) refractory DTC (RRDTC) [1-3].

Fibroblast activation protein inhibitors (FAPI)-labelled with positron-emitters are used to visualize cancer-associated fibroblast in tumour microenvironment for different diseases [4]. The novel $^{18}$F-labelled-FAPI-ligand offers promising imaging properties. Advantages are the longer physical half-life, possibility of high-volume production per synthesis (i.e., lower cost) and the superior, physical/imaging, characteristics of $^{18}$F compared to gallium-68 ($^{68}$Ga) [5].

Although providing rather low uptake values in thyroid cancer (TC) compared to sarcoma or pancreatic cancer [4], FAPI PET studies in DTC are already published [6-10]. These studies report advanced imaging properties of FAPI PET in DTC at different disease stages [6, 8, 10]. However, the majority of previous studies included heterogeneous patient collectives with mostly RAI-responsive DTC, surprisingly comparing FAPI PET in first line to $^{18}$F-FDG PET but not to the gold standard RAI whole-body scintigraphy and single photon emission computed tomography/computed tomography (SPECT/CT) [6, 8, 10]. In detailed subgroup analysis of RRDTC patients, two studies reported no significant differences between the gold standard $^{18}$F-FDG and FAPI PET [6, 8].

We hereby aimed at shedding light on the RRDTC patient's subgroup, underestimated in conclusions and headlines of most previous reports. In this interim report of a prospective trial, we performed a head to head comparison between $^{18}$F-FAPI-74 and gold standard $^{18}$F-FDG PET/CT in RRDTC with negative high dose post-therapeutic RAI whole body scintigraphy patients.

## Subjects and Methods

### Patients and study protocol

Ten patients with increasing Thyroglobulin (Tg) levels or evidence of loco-regional recurrence, lymphatic involvement, or distant metastases in morphological imaging (ultrasound/CT/magnetic resonance imaging (MRI)) with negative high-dose post-therapeutic RAI-imaging were recruited for this prospective study between 11/2020-06/2023. Exclusion criteria were: age below 18 years, RAI-responsive disease or stable disease, as defined by stable Tg levels. All patients underwent standard treatment for DTC, including total thyroidectomy and RAI-therapy, followed by levothyroxine suppression [2]. To localize iodine-131 ($^{131}$I)-negative tumour recurrence, $^{18}$F-FDG PET/CT was performed as standard of care along with additional $^{18}$F-FAPI-74 PET/CT within two weeks.

The trial was approved by the Cypriot national ethics committee and Cyprus Pharmaceutical agency (file number ΕΕΒΚ/ΕΠ/2021/48 and EudraCT-number 2021-002904-11 respectively) in accordance with the declaration of Helsinki. Informed consent was obtained from all participants.

### $^{18}$F-FDG PET/CT

Prior to the $^{18}$F-FDG administration patients were required to fast for 4 hours and avoid strenuous exercise for at least 6 hours. In all cases, the patients' serum glucose level was recorded following its measurement using a calibrated and validated glucose meter. Following the radiopharmaceutical administration, patients were intravenously hydrated with normal saline through the same venous access for 50-60 minutes while resting in order to assist both with normal tissue activity clearance and minimizing muscle uptake while maintaining and optimising tracer uptake in the target structures. Imaging was performed using the four ring GE-DiscoveryTM-IQ2-PET/CT (GE Healthcare, Milwaukee, WI). The scanner is accredited by EANM Forschungs GmbH for all EARL $^{18}$F-standards. Images were acquired 60 minutes post-injection of median: 273MBq $^{18}$F-FDG (range: 190-373). Acquisition consisted of 2 consequent PET/CT acquisitions (one straight after the other). Initially, a CT neck/upper mediastinum scan with arms parallel to the body was performed, followed by an emission scan of this region. Subsequently, whole-body imaging was performed with elevated arms. A low-dose CT in the standard end-expiratory position was acquired for attenuation-correction and correlation purposes.

### $^{18}$F-FAPI-74 PET/CT

Fluorine-18-FAPI-74 PET/CT was performed on the same scanner without specific patient preparation. Images were acquired 60 minutes post-injection with median injected dose: 234MBq $^{18}$F-FAPI-74 (range: 181-359). The imaging protocol was adapted from $^{18}$F-FDG PET/CT with a dedicated neck-scan followed by whole-body imaging.

The two PET/CT scans for each patient were performed within two weeks. In both cases, the images were reconstructed according to the accredited EARL $^{18}$F-Standard-2 parameters to ensure the harmonization of qualitative and quantitative results.

### Image analysis

All exams were read in consensus by three board-certified nuclear medicine physicians (WR, IT, AV), experienced in PET/CT of TC patients. Fluorine-18-FAPI-74 and $^{18}$F-FDG PET were reviewed separately. Fluorine-18-FAPI-74 PET/CT was analysed first to avoid bias from current gold-standard $^{18}$F-FDG PET/CT. Lung lesions were evaluated separately on CT in inspiration. Presence and number of PET-positive lesions (local recurrence, lymph node-, lung-, bone metastases) were assessed. Maximum and mean standardized uptake value (SUVmax, SUVmean) were measured for lesions with visually increased uptake above background. The volume of interest was drawn with a threshold of 40% of SUVmax and then manually adapted according to the lesion size in morphological imaging. Tumour to background ratios (TBR) were calculated with aorta SUVmean as reference region extracted from a volume of interest drawn in the descending thoracal aorta, using either SUVmax (TBRmax) or SUVmean (TBRmean) of the tumour.

### Management change

Referring physicians were asked if additional $^{18}$F-FAPI-74-PET/CT had an impact on clinical management on a per-patient basis.

### Standard of reference

Consensus characterization of every lesion based on all available previous and follow-up imaging examinations served as the standard of reference. For all patients at least one follow-up examination 3-6 months after inclusion was available. A single histopathology specimen for each patient was available to prove RRDTC diagnosis.

### Statistics

The McNemar-test was used for binary variables analysis. Quantitative uptake values of $^{18}$F-FAPI-74 and $^{18}$F-FDG PET groups were compared with Mann-Whitney U-test. Spearman correlation coefficient was used for correlation analysis between quantitative variables. P-value $<0.05$ was considered statistically significant.

## Results

### Patient-based analysis

Following the standard of reference, 4 patients did not show morphological or metabolic tumour burden in all imaging modalities (Figure 1, Table 1). In the remaining 6 patients, $^{18}$F-FDG PET correctly identified tumour recurrence whereas $^{18}$F-FAPI-74 PET missed recurrence in one patient, missing at least one $^{18}$F-FDG positive lesion in another three patients (Figure 2). In none of the patients additional $^{18}$F-FAPI-74 PET resulted in management change.

In patients #6 and #8, $^{18}$F-FAPI-74 PET/CT signal was hampered by postoperative changes. In patient #6, follow-up did not reveal local recurrence as initially suspected by $^{18}$F-FAPI-74 PET/CT. No specific therapy for the suspicion of local recurrence was initiated due to negative $^{18}$F-FDG PET/CT; however, the patient was treated for lung metastases. In patient #8, $^{18}$F-FAPI-74 PET/CT positive tumour volume was su-

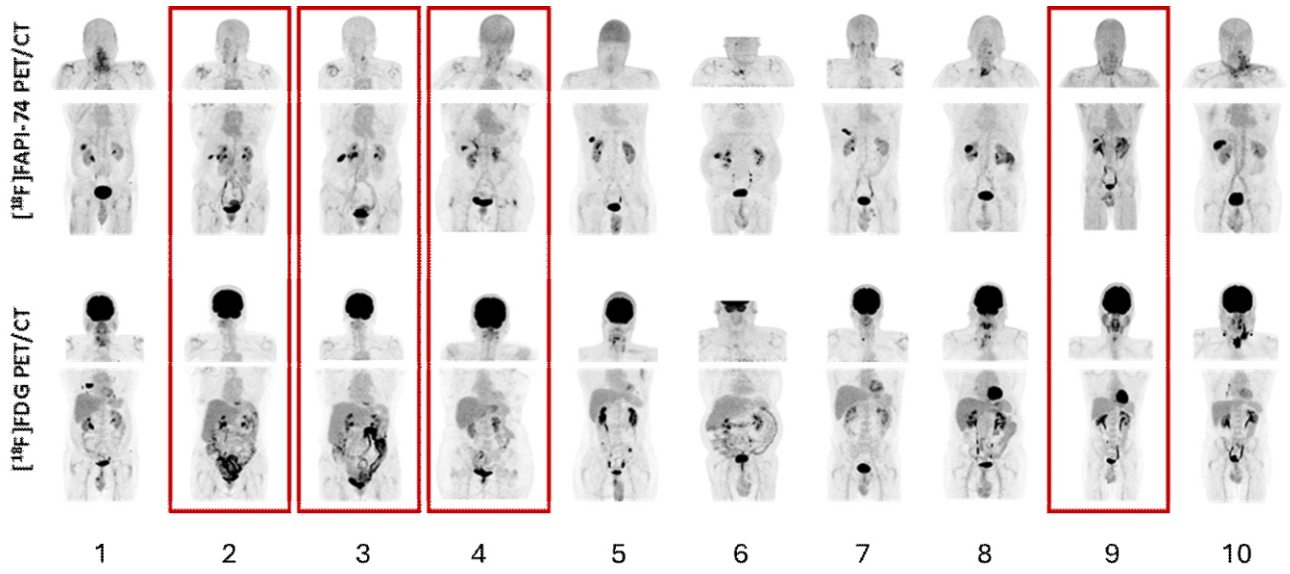


**Figure 1.** Maximum-intensity projection (MIP) of $^{18}$F-FAPI-74 and $^{18}$F-FDG PET/CT of all patients. In red outline, the four patients (2, 3, 4 and 9; matching with Table 1 numbering) without morphologic or metabolic tumour burden on both imaging modalities.

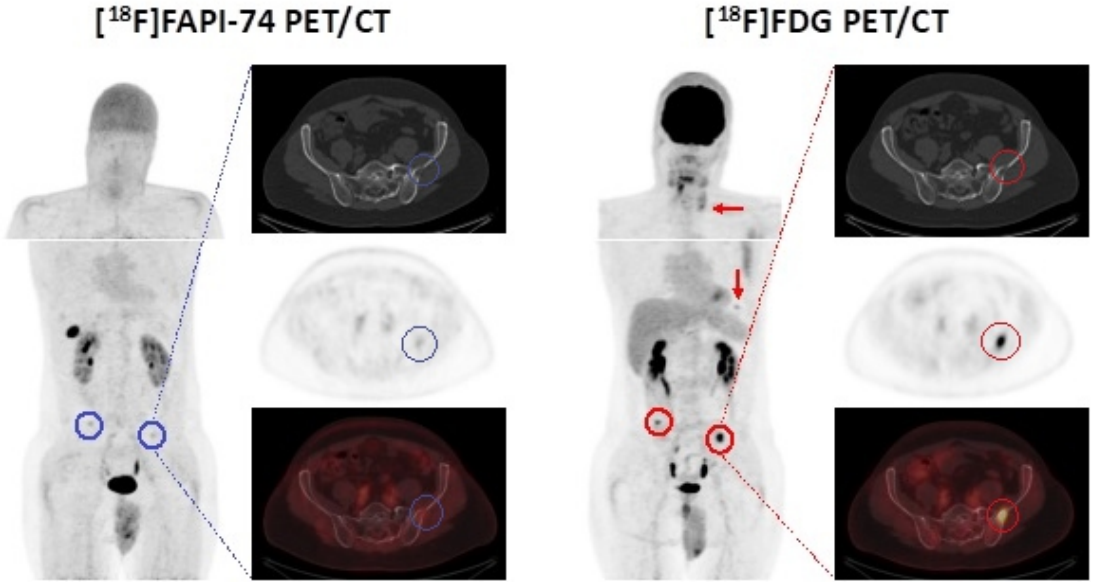


**Figure 2.** Maximum-intensity projection (MIP) and axial $^{18}$F-FAPI-74 PET/CT (A) showed low uptake in two bone metastases (blue ring): Computed tomography with a lytic lesion in left Os ileum, $^{18}$F-FAPI-74 PET and fused image with minimal uptake. Physiological $^{18}$F-FAPI-74 uptake in the gall-bladder next to the right kidney. Maximum-intensity projection and axial $^{18}$F-FDG PET/CT (B) demonstrated high uptake in the two bone lesions (red rings) and two additional bone metastases not detected in $^{18}$F-FAPI-74 PET/CT (red arrows).

perior to $^{18}$F-FDG PET/CT. Underlying morphological tumour masses (CT) correlated well with $^{18}$F-FDG uptake, suggesting that elevated $^{18}$F-FAPI-74 positive volume was partly associated with postoperative changes.

## Survival analysis

Regarding the location of the detected malignant lesions, local recurrence was detected in three out of ten patients (30%) while lymph node, bone and lung metastases were detected in four (40%), one (10%) and three (30%) patients respectively. Lesions detected by at least one of the tracers were included into the final analysis, resulting in a cohort of seventy-one lesions. Within the total cohort distribution, three of them were related to local recurrence (4.2%), twelve were lymph node metastases (16.9%), one lesion corresponded to a bone metastasis (5.6%) and fifty-two represented lung metastases (73.2%).

Fluorine-18-FDG PET/CT performed significantly better with detection rate: 40.8% (29/71) for all lesions compared to $^{18}$F-FAPI-74 PET/CT: 18.3% (13/71), (P<0.001). All $^{18}$F-FAPI-74 PET-positive lesions were also $^{18}$F-FDG-positive (Figure 3). Excluding pulmonary metastases (gold-standard CT), detection rates was 89.5% (17/19) for $^{18}$F-FDG PET/CT and 68.4% (13/19) for $^{18}$F-FAPI-74 PET/CT (P=0.125).

***Table 1.*** *Patients' characteristics.*

| ID-Gender | Histology | Cumulative $^{131}$I-dose [GBq] | Thyroglobulin [ng/mL] | Thyroglobulin-antibodies [IU/mL] | Recurrence Location | $^{18}$F-FDG / $^{18}$F-FAPI | Recurrence Confirmation |
|---|---|---|---|---|---|---|---|
| 1-male | HCTC | 9.9 | 8175.0 | Negative | Lung | +/+ | Follow-up |
| 2-female | PTC | 15.2 | 6.0 | Negative | None | -/- | Follow-up |
| 3-female | PTC | 15.2 | N/A | Unknown | None | -/- | Follow-up |
| 4-female | PTC | 10.3 | N/A | Unknown | None | -/- | Follow-up |
| 5-male | PTC | 24.8 | 663.8 | Negative | Bone | +/+ | Follow-up |
| 6-male | PTC | 11.3 | 507.0 | Negative | Lymph node/lung | +/- | Follow-up |
| 7-male | HCTC | 10.0 | 63.3 | Negative | Local | +/- | Follow-up |
| 8-male | PTC | 5.1 | 679.0 | Negative | Local/lymph node | +/+ | Follow-up |
| 9-male | PTC | 7.9 | 3.36 | Negative | none | -/- | Follow-up |
| 10-male | PTC | 2.1 | 15.6 | Negative | Local/lymph node | +/+ | Pathology |

*Last therapeutic $^{131}$I-whole body scan (WBS): negative for all patients. Patients' age: 40-81. PTC; Papillary thyroid cancer, HCTC; Hürthle cell thyroid cancer.*

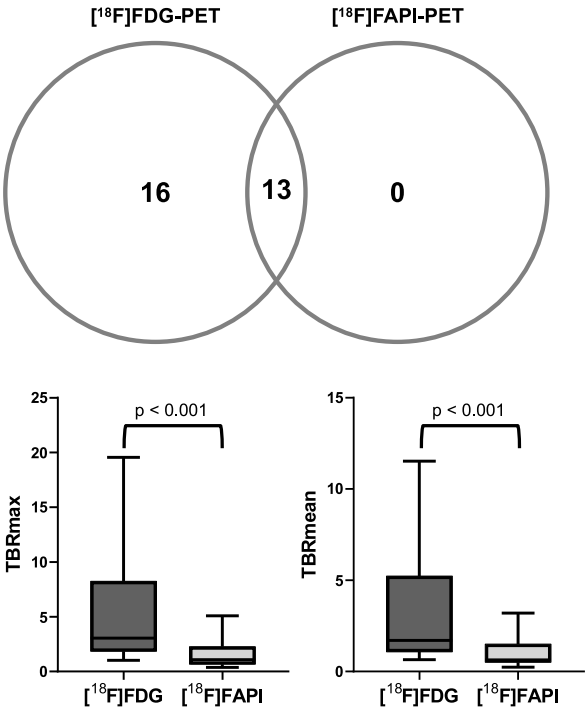


**Figure 3.** Two-way Venn diagram of the detection of $^{18}$F-FAPI-74/$^{18}$F-FDG PET+ lesions (n=29). Box plots for quantitative uptake-values TBRmax/TBRmean; significantly higher values for $^{18}$F-FDG versus $^{18}$F-FAPI-74 (P<0.001).

There was a significant correlation between $^{18}$F-FDG and $^{18}$F-FAPI-74 uptake (TBRmax: rs=0.75; P<0.001; TBRmean: rs=0.71; P<0.001). However, quantitative uptake values were significantly higher for $^{18}$F-FDG than $^{18}$F-FAPI-74 in all metastases ($^{18}$F-FDG: median TBRmax: 3.05 (1.02-9.55), $^{18}$F-FAPI-74: median TBRmax: 1.09 (0.38–5.09); P<0.001) ($^{18}$F-FDG: me-dian TBRmean: 1.71 (0.65-11.53), $^{18}$F-FAPI-74: median TBRmean: 0.64 (0.24-3.20). Due to low patient number, subgroup analysis for different organs is not reported.

## Discussion

In this prospective trial on the head-to-head $^{18}$F-FAPI-74 and $^{18}$F-FDG PET/CT comparison in RRDTC patients, $^{18}$F-FDG PET/CT corroborates its role as gold standard imaging method in this patients' group.

Fluorine-18-FAPI-74 PET/CT missed recurrence in one patient. In another three patients, $^{18}$F-FDG PET/CT detected more metastases than $^{18}$F-FAPI-74 PET/CT. This FAPI-PET/CT performance is inferior to previously reported detection rates and accuracy in very heterogeneous collectives of recurrent DTC patients with mainly RAI-responsive disease [6, 8]. Sayiner et al. (2023) reported on a per patient detection rate of 72% for $^{18}$F-FDG PET/CT and 86% for FAPI-PET/CT [6]. Fu et al. (2022) showed a significantly improved sensitivity for FAPI-PET/CT in neck lesions (83% vs 65% for $^{18}$F-FDG) and distant metastases (79% vs 59% for $^{18}$F-FDG) [8]. The inferiority of $^{18}$F-FDG PET/CT in these studies with mixed collectives with a majority of RAI-responsive disease is however expected, as $^{18}$F-FDG PET/CT is recommended primarily in RAI-negative DTC [1, 2]. When looking at the data reported for the subgroup of RRDTC patients, Sayiner et al. (2023) and Fu et al. (2022) showed non-significant differences between FAPI- and $^{18}$F-FDG PET/CT on a per patient (75% vs 75%) [6] and per lesion basis (57% vs 43%) [8], however utilizing a different FAPI-compound [6, 8].

Previous studies did not report on quantitative uptake values in RRDTC subgroup. Interestingly we report significantly higher uptake values for $^{18}$F-FDG- than $^{18}$F-FAPI-74 PET/CT. This is in line with previously published results by Mu et al. (2003) with a median SUVmax of 2.6 for $^{18}$F-FDG PET/CT versus 2.1 for FAPI-PET/CT for all lesions [10]. In contrast Mu et al. (2023) report on significant higher uptake values for FAPI-PET/CT in lymph node metastases and local recurrence [10]. These results are partly supported by Fu et al. (2022) with significant higher uptake values for FAPI-PET/CT-in lymph node metastasis, except of the central compartment (non-significant), however not for local recurrence [8]. Subanalysis for uptake values and different tumour locations was not performed in our study due to the limited patient number. For lung lesions results are contradictory, as Mu et al. (2023) report on significant higher values for $^{18}$F-FDG PET/CT (SUVmax 2.2 vs. 1.3 for FAPI-PET) [10], but Fu et al. (2022) report on significant higher values for FAPI-PET/CT (SUVmax 1.7 vs. 1.1 for $^{18}$F-FDG PET/CT) [8]. These results with relatively low uptake values of both tracers in lung metastases underline the role of lung-CT as gold standard method for the assessment of lung metastases in RRDTC patients [3]. This is reflected by higher detection rate in extra-pulmonary tumour recurrence of RRDTC for $^{18}$F-FDG- and $^{18}$F-FAPI PET/ CT in our study.

Thyroid cancer FAP-expression depends on tumour size, extra-thyroidal extension, the presence of lymph node metastases and dedifferentiation [11, 12]. This might explain the limited FAPI uptake in small lesions (e.g., lung metastases) reported by previous studies and shown in our results [8, 10].

Management change is an important factor for clinical acceptance of a novel diagnostic method. In RRDTC patients, $^{18}$F-FDG PET/CT induces a management change in 40% [3]. It seems reasonable that additional FAPI-PET/CT, like other imaging methods, may struggle to further improve this gold standard. In other tumour entities, FAPI-PET/CT initiates management change compared to standard of care in up to 25% as reported by Kosmala et al. (2023) [13]. However, this includes mainly $^{18}$F-FDG-"problematic" tumours (HCC, pancreatic-Ca) with treatment modification in 6 out of 8 patients (75%) [13]. A significant fraction of RRDTC presents with negative $^{18}$F-FDG PET/CT. Using additional molecular imaging in these patients is reasonable for more precise staging [14]. This was also reported for other tracers ($^{68}$Ga-dodecanetetraacetic acid-tyrosine-3-octreotate (DOTATATE)) [15]. A potential gatekeeper role for theragnostic approaches might also be discussed for FAPI-PET/CT, as already shown for somatostatin receptors-targeting tracers [16]. Currently, reports on FAPI-therapy in RRDTC with beta-emitting-compounds are still case-reports restricted [17].

Our study limitations are its small patient number and relatively high number of lung metastases compared to other locations in the lesion-based analysis. However, RRDTC is a rare disease status with impaired outcome compared to RAI-responding patients. In thyroid cancer patients with metastatic disease additional biopsy at time of progression is not a routine procedure. Therefore, histopathological confirmation is only available in one patient. Dedicated sub studies are needed to reduce confounders in heterogeneous groups. Many different $^{68}$Ga/$^{18}$F-labelled FAPI-compounds used in previous studies having however similar imaging properties [5, 18]. Furthermore, to the $^{18}$F-labelled-compounds superior imaging capabilities over $^{68}$Ga-labelled-compounds, the advantage of high-volume production and longer half-life creates additional logistic and economic benefits.

*In conclusion,* in this prospective study $^{18}$F-FDG PET/CT corroborates its role as a gold standard in RRDTC patients. Efforts should be made for FAP-ligands usage to complement in $^{18}$F-FDG-negative disease and as potential gatekeeper for radioligand therapy.

*The authors declare that they have no conflicts of interest*

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**Ethics approval**
The trial was approved by the Cypriot national ethics commit-

tee and Cyprus Pharmaceutical agency; file number ΕΕΒΚ/ΕΠ/2021/48 and registered in the EudraCT trial registry with the number 2021-002904-11 (registered 23/09/2021) respectively; in accordance with the declaration of Helsinki. Informed consent was obtained from all participants.

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